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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,314	04/11/2005	Sakayu Shimizu	21147 (C038435/0178882)	2382

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EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,314	SHIMIZU ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11,13,16,17 and 19* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *10,11,13,16 and 17* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 10-17 and 20-21 were examined in the previous action. With supplemental amendment of this application, the applicant, on dates 5/24/06, amended claim 10 and cancelled claims 12, 14, 15, 20 and 21. Claim 1-9 and 19 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected claims, there being no allowable generic or linking claim.

Claim Rejections

35 U.S.C 112

> The following is a quotation of the second paragraph of 35 U.S.C. 112: The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Claim 13 (depending on claim10) is confusing as claim 10 is limited to the NADPH dehydrogenase gene of the OYE2 or OYE3 gene of Saccaromyces cerevisiae s288c but claim 13 say the enzyme is derivable from other species of Saccharomyces or other genera.

35 U.S.C 112

1. Written Description requirement

Applicants arguments against rejection of claims 10-14, 16-17, 20-21 under 35 U.S.C. 112, first paragraph written description are acknowledged. Rejection of claims under 35 U.S.C. 112, first paragraph written description was withdrawn in view of applicants arguments/ amendments.

III. *Enablement requirement*

Applicants arguments against rejection of claims 10-14, 16-17, 20-21 under 35 U.S.C. 112, first paragraph enablement requirement are acknowledged. Rejection of the claims under 35 U.S.C. 112, first paragraph enablement requirement was withdrawn in view of applicant's arguments/ amendments.

IV CLAIM Rejection - 35 U.S.C 102

The rejections of claims 10-12, 13-14 and 16-17 under 35 USC 102 using Fukuoka et al. of the previous office action became moot because of applicants amendment of the claim 10 and cancellation of claims 12 and 14.

Applicants argument for withdrawal of Kataoka et al. (Biosci.biotec. biochem. 2002, 66, pp 2651-2657) not being prior art is considered. 35 USC 102 rejection using Kataoka et al. (Biosci.biotec. biochem. 2002, 66, pp 2651-2657) is withdrawn.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 11, 13, 16 and 17 are rejected under 35 U.S.C. 103(a) by Vaz et al. (Biochem. 1995, 34, 4246-4256) in view of Fukuoka (EP1074630) and Niino et al. (JBC 1995, 270, 1983-1991).

Vaz et al. (Biochem. 1995, 34, 4246-4256) teach the use of old yellow enzymes (NADPH dehydrogenase) from yeast (*S. carisbergensis*) for the reduction of olefinic bond (ketoisophorone) and also teach the expression of OYEs (including oye2 and oye3) from S. cerevisiae in E. coli.

Fukuoka et al. teach the use of immobilized microorganisms (various yeasts to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60^0 C. Fukuoka et al. state that *S. cerevisiae* is used to convert ketoisophorone to levodione (Page 2), although the production of levodione is low. To improve the production Fukuoka et al. used various yeast strains in immobilized form.

Niino et al. (JBC 1995, 270, 1983-1991) teach genes of OYE-2 and OYE-3 from S. cerevisiae and transformed E. coli expressing these genes and also teach said OYE2 and OYE3 reduce the olefinic bond of cyclohexenone to produce cyclohexanone (although not specifically reduction of olefinic bond in cyclohexenone ring of ketoisophorone (conversion to levodione)).

One skilled in the art would be motivated to use transformed microorganisms or cell free extract thereof (crude OYE2 or OYE3) since transformed microorganisms (transformed with OYE genes) or cell free extract thereof would be expected to have more active enzymes compare to S. cerevisiae (as referred in Fukuoka et al.)) instead of S. cerevisiae for the reduction of olefinic bond of ketoisophorone to yield levedione.

As such it would have been obvious to one of ordinary skill in the art to use transformed microorganisms (*E. coli*) or cell free extract thereof taught by Niino et al. which express the OYEs as taught by Vaz et al to catalyze the conversion of ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60^0 C as taught by Fukuoka et al.

Applicant's argument against 103 rejection is considered but not found persuasive as explained above and below:

Applicant argue that

(1) Rejection lacks a clearly explained motivation to combine the arts recited in the 103(a) rejection;

(2) Fukuoka on page 2 teach away from combination by stating that baker's yeast is not suitable for the use;

(3) Rejection fails to clearly delineate differences between the prior art and the claimed invention;

(4) Even if the three references that combined in 103(a) rejection one does not get the claimed invention since Vaz et al do not show that *S. cerevisiae* S288c OYE2 and OYE3 convert ketoisophorone to levadione and on applicant opinion neither Fukuoka nor Niino fill this gap.

The answer against the above 4 arguments is:

In view of the above characteristics of the all OYEs (i.e. conversion α,β unsaturated ketone to ketone via reduction of olefinc bond) , homology of all three OYEs as well as specific showing that *S. cerevisiae* is capable of converting ketoisophorone to levadione as discussed above skilled artisan would expect that both oye2 and oye3 would convert ketoisophorone to levedione.

The prior art clearly teaches that

(1) All OYEs (OYE1, OYE2 and OYE3) catalyze the reduction of olefinic bond of α,β unsaturated ketone, such as convert cyclohexenone to cyclohexanone (Vaz et al and Niino et al.).

(2) Microorganisms (such as E. coli) or cell free extract thereof (merely crude enzyme) transformed with OYEs genes (Vaz et al, Niino et al.) also catalyze the reduction of olefinic bond of α,β unsaturated ketones .

(3) Microorganisms having OYEs (Fukuoka et al.) convert ketoisophorone to levodione. In view of all of the above, it would have been obvious to those knowledgeable in the art that transformed microorganism expressed with OYE2 and OYE3 or cell free extract thereof (merely crude enzyme) will convert ketoisophorone to levodione, since *S. cerevisiae* themselves do convert ketoisophorone to levodione. OYEs have been shown by the art to be the enzymes responsible for this activity in other organisms, and OYE2 and OYE3 are highly homologous to OYE1 and produced by *S. cerevisiae*

Applicant's arguments against 103(a) rejection are considered but not found persuasive as explained above and bellow:

(1) one of skill in the art would have clearly been motivated to use transformed microorganism or cell free extract thereof (merely crude enzyme) (taught by prior art) to convert ketoisophorone to levodione **because**

1) transformed microorganisms (E. coli) expressed with OYE2 or OYE 3 gene or cell free extract thereof (merely crude enzyme) has the OYE2 or OYE3 activity and hence will be expected to convert ketoisophorone to levodione (inherent property of OYEs).

2) To have better control in the method of conversion of ketoisophorone to levedione (compare S. cerevisiae) one will motivated to use transformed microorganisms or cell free extract thereof (merely crude enzyme) since microorganisms transformed with OYE genes would have more active enzymes compare to *S. cerevisiae* as one would expect recombinant expression to result in much higher levels of OYE2or OYE3 ennzyme in the recombinant host than the naturally found in *S. cerevisiae* .

Applicants argument that Fukuoka teach away from cited combination is wrong as Fukuoka (Fukuoka p.2) in same paragraph cited by applicant teach the use of *S. cerevisiae* for the conversion of ketoisophorone to levedione, Fukuoka "teaching away" is based on the low level of activity in *S. cerevisiae*. However, it is immaterial whether production is low or not, *S. cerevisiae* do convert ketoisophorone to levedione. Examiner did not suggest the use of *S. cerevisiae* but instead suggested use of E. coli or other microorganism transformed with the *S. cerevisiae* OYE2 or OYE3 genes. As skilled artisan would clearly expect such recombinant production would in fact remedy the disadvantage of using natural *S. cerevisiae* as over expression of enzyme would be expected to substantially increase the activity.

The prior art teaches that microorganisms transformed or not transformed which contain OYEs or cell free extract thereof (merely crude enzyme) do convert ketoisophorone to levodione. Prior arts as recited above (numerous others in the literature) suggest that OYEs and vehicles containing OYEs (" transformed microorganism" or cell free extract thereof (merely crude enzyme) convert α,β unsaturated ketone to ketone (ketoisophorone to levedione is one of such a conversion) via reduction of olefinc bond. Therefore there is a **prima facie case of unpatentibility** of applicants' invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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